Drugs for Acid Peptic Diseases

Acid peptic diseases are common gastrointestinal disorders, which include gastroesophageal reflux disease, peptic ulcers, non-ulcer dyspepsia and stress-related gastric mucosal injury. Drugs commonly used in the management of these disorders include antacids, H₂ blockers, proton pump inhibitors and mucosal protective agents. In this chapter, pharmacology of these drugs will be discussed, followed by brief description of their roles in the management of common acid peptic diseases.

Overview of Peptic Ulcer Disease

Acid peptic diseases are a group of disorders that involve erosion or ulceration of the mucosal lining of the gastrointestinal tract. Gastroesophageal reflux disease (GERD), gastric and duodenal peptic ulcers, non-ulcer dyspepsia and stress-related gastric mucosal injury are included in acid peptic diseases. Use of NSAIDs (non-steroidal anti-inflammatory drugs) and H. pylori infection account for ~ 90 % of peptic ulcers.

Relevant aspects of gastrointestinal physiology
A relative imbalance between damaging factors and defensive factors of the gastrointestinal mucosa is important in the pathogenesis of peptic ulcer disease.

Damaging factors include acid, pepsin, bile, NSAIDs etc., while defensive factors include mucus secretion, bicarbonate secretion, mucosal blood flow, prostaglandins and repair processes following mucosal injury.

In the stomach, acid (H⁺) is secreted by the proton pump (H⁺/K⁺-ATPase) located on the canalicular surface of the parietal cells in the gastric mucosal lining.

The parietal cells contain receptors for histamine (H₂ receptors), gastrin (CCK-B receptors) and acetylcholine (muscarinic M₃ receptors). Their stimulation increases the secretion of acid by the parietal cells.

Stimulation of enterochromaffin (ECL) cells by gastrin and acetylcholine also release histamine from them, which in turn stimulates parietal cells to secrete acid.

### Drugs Used in Acid Peptic Diseases

#### Classification

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### Antacids

Antacids are weak bases that reduce gastric acidity by reacting with gastric hydrochloric acid (HCl) and thereby forming salt and water. Many of them are available as over-the-counter formulations, however, acid-neutralizing capacities of different formulations are highly variable.
Antacids should not be taken within 2 hours of consumption of drugs such as iron, tetracyclines, fluoroquinolones and itraconazole as they interfere with absorption of these drugs.

**Magnesium hydroxide (Milk of magnesia, Mg(OH)₂):**
- It reacts with HCl to form magnesium chloride (MgCl₂) and water
- Unabsorbed magnesium salts cause osmotic diarrhea

**Aluminium hydroxide (Al(OH)₃):**
- It reacts with HCl to form aluminum chloride (AlCl₃) and water
- Unabsorbed aluminum salts have constipating effect

Due to laxative and constipating effects of magnesium and aluminum salts respectively, magnesium hydroxide and aluminum hydroxide are frequently combined in proprietary combinations.

**Sodium bicarbonate (NaHCO₃):**
- It reacts with HCl to form sodium chloride and carbon dioxide.
- Carbon dioxide causes belching and gastric distension, while sodium chloride may worsen fluid retention in patients with hypertension, heart failure and renal failure.
- Unreacted bicarbonate may produce metabolic alkalosis due to its ready absorption.
- Its excessive use along with excess of dairy products can cause hypercalcemia, renal failure and metabolic alkalosis (milk-alkali syndrome).

**Calcium carbonate (CaCO₃):**
- It is less soluble than sodium bicarbonate and reacts slowly with HCl to form calcium chloride and carbon dioxide.
- Important side effects are belching, metabolic alkalosis and milk-alkali syndrome with excess consumption of dairy products.

**H₂ blockers (H₂-receptor antagonists)**

They competitively inhibit H₂ receptors at gastric parietal cells and reversibly inhibit secretion of acid in dose-dependent manner. They especially inhibit nocturnal acid secretion more effectively than meal-stimulated acid secretion.

All H₂ blockers undergo significant first-pass hepatic metabolism except nizatidine. All H₂ blockers except nizatidine are available in formulations for intravenous administration. Famotidine is the most potent H₂ blocker. Dose reduction is required in moderate-severe renal insufficiency and in possibly severe hepatic insufficiency.

**Adverse effects of H₂ blockers:**
- H₂ blockers are very safe; common adverse effects are headache, myalgia, fatigue, diarrhea and constipation.
- Rare adverse effects are blood dyscrasias and blockade of cardiac H₂ receptors (especially by intravenous administration) causing bradycardia and hypotension; therefore intravenous injections are given in intervals over 30 minutes.
- Intravenous H₂ blockers, especially cimetidine, may cause agitation, confusion, hallucinations, etc., especially in elderly patients or those with
renal or hepatic insufficiency.
- In critically ill patients, intravenous H₂ blockers may increase the risk of nosocomial pneumonia.

Cimetidine:
- With high doses or prolonged use, it can cause antiandrogenic side effects like gynecomastia or impotence in men and galactorrhea in women by inhibiting binding of dihydrotestosterone to androgen receptors, inhibiting estradiol metabolism and increased serum prolactin levels.
- It prolongs the half-lives of drugs like warfarin, phenytoin and clopidogrel by interfering with hepatic cytochrome P450 pathways.

Proton pump inhibitors (PPIs)
- PPIs are lipophilic weak bases that are administered as inactive prodrugs and in delayed release formulations.
- A PPI is absorbed from intestinal mucosa and diffuses readily into parietal cell canaliculi, where it becomes protonated and is concentrated by Henderson-Hasselbalch trapping. Here it is converted into its active form which irreversibly inactivates H⁺/K⁺-ATPase.
- Esomeprazole is an S-isomer of omeprazole, while dexlansoprazole is an R-isomer of lansoprazole.
- Esomeprazole and pantoprazole are also available in formulations for intravenous administration.
- PPIs are usually administered ~1 hour before breakfast/meal; their acid inhibiting effects last for ~24 hours and maximum effectiveness is achieved after 3—4 days of administration.
- PPIs undergo hepatic metabolism but have negligible renal clearance; hence dose reduction is not required in renal insufficiency or in mild-moderate hepatic dysfunction.
- PPIs inhibit both fasting and meal-stimulated acid secretion and inhibit 90—98% of a 24-hour acid secretion; therefore they are very effective in management of gastrinoma and other conditions with acid hypersecretion as compared to other classes of drugs.

Adverse effects of PPIs:
- PPIs are very safe; common adverse effects are headache, diarrhea and abdominal pain. Rarely, cases of acute interstitial nephritis have been reported.
- By reducing acid secretion, PPIs may reduce absorption of vitamin B₁₂ and calcium; hypomagnesemia has also been reported. Those requiring a long-term PPI treatment and are at risk of osteoporosis should be monitored for bone density and should be given calcium supplements.
- In patients taking PPIs, increased risk of community-acquired pneumonia, nosocomial pneumonia, clostridium difficile infection and other enteric infections have been reported.
- ~3% of patients taking PPIs develop hypergastrinemia, which normalizes within 4 weeks of stopping the drugs. Enterochromaffin-like (ECL) cell hyperplasia has also been reported, but carcinoid tumor formation is not observed. Small benign gastric fundic-gland polyps have been noticed in some patients following long-term PPI intake.
Important drug interactions with PPIs:

- PPIs interfere with the absorption of drugs like ketoconazole, itraconazole, digoxin, etc., by reducing gastric acidity.
- PPIs (except rabeprazole and pantoprazole) may reduce antiplatelet action of clopidogrel by reducing its activation.
- Rabeprazole and pantoprazole do not have significant drug interactions.
- Omeprazole may inhibit the metabolism of phenytoin, diazepam and warfarin.
- Esomeprazole inhibits the metabolism of diazepam.
- Lansoprazole enhances the clearance of theophylline.

Mucosal protective agents

Sucralfate:

- Sucralfate is an **aluminum sucrose sulfate** which acts by forming viscous tenacious paste in water or acidic solutions; it selectively binds to **erosions or ulcers** for up to 6 hours. Negatively charged sucrose sulfate, a breakdown product of sucralfate, binds to positively charged proteins in the base of ulcers or erosions.
- It also stimulates the secretion of mucosal bicarbonate and prostaglandins.
- It is administered four times a day ~1 hour before meals.
- There are no systemic side effects due to lack of systemic absorption. Because of the content of aluminum salt, an important side effect is **constipation** and it should not be used for prolonged duration in **renal insufficiency**.
- It reduces absorption of many drugs by binding with them.

Prostaglandin analogs:

- Misoprostol is a **PGE**, analog with mucosal protective and acid inhibitory actions. It stimulates the production of mucus and bicarbonate as well as increases mucosal blood flow.
- It is used to prevent NSAID-induced ulcers, but it requires 3—4 times dosing per day.
- Important adverse effects are **diarrhea** and **abdominal cramps**.
- As it stimulates uterine contractions, it is not used during pregnancy and requires cautious use in women of childbearing age.
- It does not have significant drug interactions.

Bismuth compounds:

- Bismuth subsalicylate and bismuth subcitrate potassium are bismuth compounds.
- Bismuth subsalicylate is rapidly dissociated in the stomach; salicylate is absorbed and excreted in urine, while 99 % of bismuth is excreted in stool. The minimally absorbed bismuth is stored in tissues and is slowly excreted in urine.
- Bismuth compounds create a **protective layer over erosions and ulcers** and protect them from acid and pepsin. They also stimulate the secretion of mucus, bicarbonate and prostaglandin.
- As salicylate inhibits the secretion of prostaglandin and chloride in the intestines, bismuth subsalicylate reduces stool frequency and liquidity in **acute infectious diarrhea**.
- Bismuth also has direct antimicrobial activity, including against **H. pylori**, and binds enterotoxins.
Bismuth compounds are used in the treatment of dyspepsia and acute diarrhea. Bismuth compounds are included in 4-drug regimens for treatment of H. pylori-associated ulcers, however, “triple therapy” regimens are considered the first-line treatment. Bismuth subsalicylate is also used in prevention of traveler’s diarrhea. Bismuth compounds are very safe; harmless blackening of stool and darkening of tongue may be noticed. Bismuth toxicity (encephalopathy) is not reported with bismuth subsalicylate or subcitrate, but prolonged use may cause salicylate toxicity.

Pharmacologic Management of Acid Peptic Diseases

Treatment of GERD

- Infrequent dyspepsia or heartburn (< 3/week) can be managed by taking an antacid or an H₂ blocker intermittently; frequent heartburn should be managed by twice daily H₂ blockers or proton pump inhibitors.
- Although antacids provide faster symptom relief, their effects are short-lasting (1—2 hours) than those of H₂ blockers (6—10 hours).
- PPIs are more effective than H₂ blockers in the management of gastroesophageal reflux disease (GERD); once-daily dosing is effective in ~ 85—90% of patients. Long-term daily maintenance of PPI is required in patients with erosive gastritis or esophageal complications of GERD, while those with extraesophageal complication of GERD should be treated via twice-daily PPI administration for at least 3 months.

Treatment of peptic ulcers

- PPIs have almost replaced H₂ blockers in the management of peptic ulcers. However, H₂ blockers, if used, are given as once-daily bedtime dose for 6—8 weeks to suppress nocturnal acid secretion.
- Most of the duodenal ulcers and gastric ulcers are healed by use of PPIs for 4 weeks and 6—8 weeks, respectively.
- Sucralfate accelerates the healing of and reduces the recurrence rate of peptic ulcers.
- Following acute gastrointestinal bleeding from a peptic ulcer, high-dose oral PPI or continuous intravenous infusion of PPI is used to reduce the risk of rebleeding.

Treatment of H. pylori-associated ulcers

- The best regimen for treatment of pylori-associated ulcers is “triple therapy” for 14 days: a PPI (twice daily), clarithromycin (500 mg twice daily) and amoxicillin (1 g twice daily); followed by a PPI once daily for 4—6 weeks. Metronidazole (500 mg twice daily) can be used in penicillin-allergic patients.
- An alternative 10-day regimen for treatment of H. pylori-associated ulcers is: a PPI (twice daily) and amoxicillin (1 g twice daily) on days 1—5, followed by a PPI (twice daily), clarithromycin (500 mg twice daily) and tinidazole (500 mg twice daily) on days 6—10.
Both 14-day or 10-day regimens should be followed by a PPI once daily for 4—6 weeks to ensure complete healing of the ulcer.

**Prevention of bleeding from stress-related gastritis in critically ill patients**

- For patients without nasoenteric tubes or with significant ileus, intravenous H$_2$ blockers are preferred over intravenous PPIs because of cost-effectiveness and proven efficacy; continuous infusion is preferred over bolus administration.
- In patients with nasoenteric tubes, immediate-release oral omeprazole is preferred over intravenous H$_2$ blockers because of cost-effectiveness and ease of administration.

**Review Questions**

The correct answers can be found below the references.

1. **Constipation is a known side effect of which of the following drugs?**
   - A. Magnesium hydroxide
   - B. Misoprostol
   - C. Omeprazole
   - D. Rabeprazole
   - E. Sucralfate

2. **Which of the following drugs causes blackening of stools?**
   - A. Aluminium hydroxide
   - B. Bismuth subsalicylate
   - C. Cimetidine
   - D. Misoprostol
   - E. Sucralfate

3. **Which of the following is the most preferred proton pump inhibitor if the patient required simultaneous administration of clopidogrel?**
   - A. Esomeprazole
   - B. Dexlansoprazole
   - C. Lansoprazole
   - D. Omeprazole
   - E. Rabeprazole

**References**


Correct answers: 1E, 2B, 3E